

Synthesis and First Molecular Structure of a Bis-2-spiro-1-boraadamantane Derivative

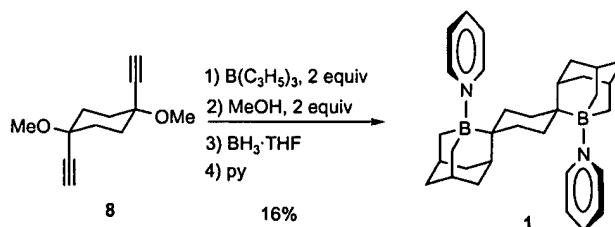
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ABSTRACT



A new method for synthesizing the 2-spiro-boraadamantane pyridine complex (2) from 1-ethynylcyclohexylmethyl ether has been developed. The chemistry has been applied to the synthesis of bis-2-spiro-1-boraadamantane-pyridine (1) from *trans*-1,4-diethynyl-1,4-dimethoxycyclohexane (8). This bis-Lewis acid serves as a self-assembling molecular building block with difunctional Lewis bases.

The allylboron condensation reaction of triallylborane with alkynes permits the efficient construction of 1-boraadamantane derivatives.¹ 1-Boraadamantane forms air-stable solid adducts with primary amines² and pyridine,³ and 1-boraadamantane derivatives can be converted to 1-adamantane,⁴ 1-homoadamantane,⁵ and 1-aza-adamantane⁶ derivatives. Our studies of the allylboron condensation reaction with alkynes have focused on developing a suitable dialkyne substrate that would lead to a bis-2-spiro-1-boraadamantane framework, as exemplified in the dipyridine adduct 1. The bis-Lewis acid

can be used as a building block to direct the self-assembly of nitrogen-containing Lewis bases.

The use of metals such as copper, palladium, zinc, and cobalt to direct the self-assembly of rationally designed Lewis bases to form supramolecular networks has been demonstrated.⁷ Additionally, the use of boron to form supramolecular structures⁸ and boron-containing polymers⁹ with Lewis bases has also been achieved. The framework of the bis-2-spiro-1-boraadamantane could potentially be applied as a self-assembling molecular building block upon the addition of an appropriate difunctional Lewis base, such as pyrazine, to give an extended supramolecular network (4) (Figure 1).

The inspiration for constructing such a framework arose from the reported synthesis of the 2-spiro-1-boraadamantane-

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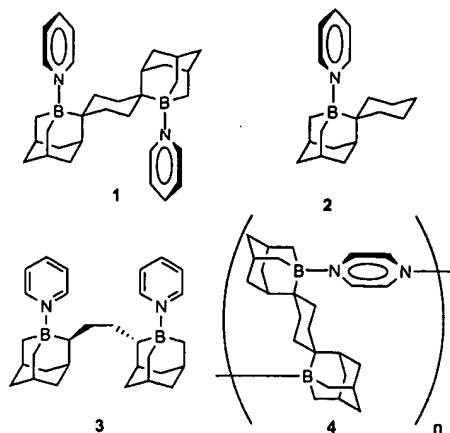


Figure 1. Targets of the allylboron condensation reaction.

pyridine (2)¹⁰ and the 2,2'-ethylenedi-1-boraadamantane-pyridine complex (3).¹¹ Mikhailov and co-workers reported the synthesis of 2 in 59% overall yield from 1-ethynylcyclohexene. Thus, a reasonable synthetic approach to the bis-2-spiro-1-boraadamantane framework in (1) could potentially follow from 1,4-diethynyl-1,4-cyclohexadiene. However, the availability of hydrocarbon precursors limits the generality of this approach. Since there is ample precedent for the synthesis of 1-boraadamantane derivatives from propargyl ether substrates, 1-ethynylcyclohexyl methyl ether (5) was selected as a model substrate for allylboron condensation in our synthetic approach to 2. In this approach, the condensation of triallylborane with 5 should give borabicyclic 6, and the hydroboration of 6 followed by the addition of pyridine should yield the pyridine adduct 2. Furthermore, if the substitution of ether 5 for 1-ethynylcyclohexene succeeds in this approach to 2, then the readily available substrate, *trans*-1,4-diethynyl-1,4-dimethoxy-cyclohexane (8), could lead to the synthesis of 1.

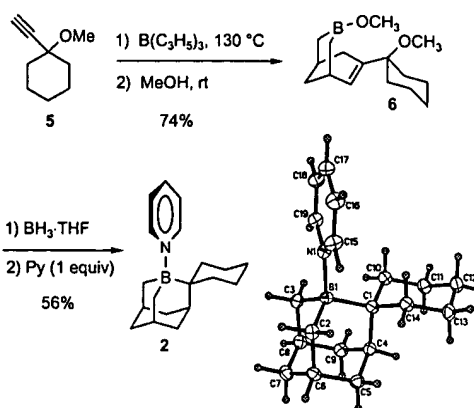
The Williamson ether synthesis was used to prepare ether 5 in 75% yield.¹² Condensation of 5 with triallylborane followed by methanolysis provides the borabicyclic 6 as a yellow viscous liquid in 74% yield after purification by vacuum distillation (108 °C, 0.05 mmHg). The hydroboration of 6 by borane·THF followed by the removal of THF results in a crude white residue. Addition of benzene to the residue forms a suspension, and the addition of pyridine to this suspension provides the 2-spiro-1-boraadamantane complex (2) in 56% yield after precipitation and filtration (Scheme 1). Recrystallization of 2 from a 1:1 solution of acetone/2-propanol affords air-stable crystals of 2 suitable for X-ray diffraction (Scheme 1).

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Scheme 1



The pyridine molecule in 2 coordinates to the 2-spiro-1-boraadamantane core in a plane parallel to the plane formed by the proximal axial hydrogen atoms and C10 or C14. This led directly to the speculation that the structure of a bis-2-spiro-1-boraadamantane-pyridine complex (1), with the boron atoms oriented *trans* on the central cyclohexane ring, would be predisposed to affix the coordinated pyridine molecules in *opposite* directions.

The rigidity imposed by the spirocyclohexane moiety could prove to be a favorable characteristic for supramolecular self-assembly. In contrast to the rigid molecular structure of 1, the crystal structure of 3 shows that the ethylene bridge permits a skewed orientation of the bridged boraadamantane cores and thus a skewed orientation of the coordinated pyridine molecules.¹³

Since 1-ethynylcyclohexyl methyl ether (5) led to the successful assembly of 2, *trans*-1,4-diethynyl-1,4-dimethoxycyclohexane (8) was selected as the appropriate substrate in our synthetic approach to 1. Prior to the synthesis of 8 and 1, a modeling study at the HF/3-21g* level of theory was performed to estimate the relative stabilities of the isomeric bis-2-spiro-1-boraadamantane frameworks (Figure 2).

The modeling study suggests that the *trans* orientation (III) of the boron atoms in a bis-2-spiro-1-boraadamantane framework is favored over the *cis* orientation (I) by 2.5 kcal/mol. Furthermore, the *trans*-diaxial III is preferred over the *trans*-diequatorial II by 5.0 kcal/mol. As expected, the axial-equatorial structure I is intermediate in energy between II and III. However, this modeling study does not take into account the subsequent coordination of Lewis basic ligands such as THF or pyridine to the Lewis acidic boron centers in the frameworks of I, II, and III. The subsequent coordination of pyridine to both boron centers in III could alter the equilibrium to favor the *trans*-diequatorial orientation of the boron centers in II.

With the results of the modeling study in hand, we proceeded with the synthesis of diyne 8. Thus, diol 7 was

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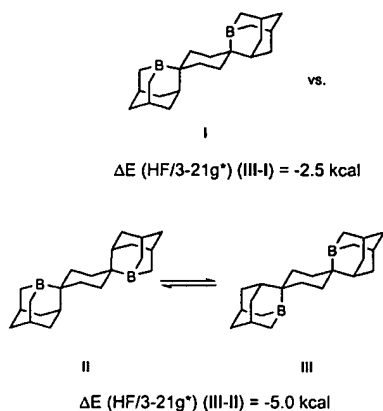
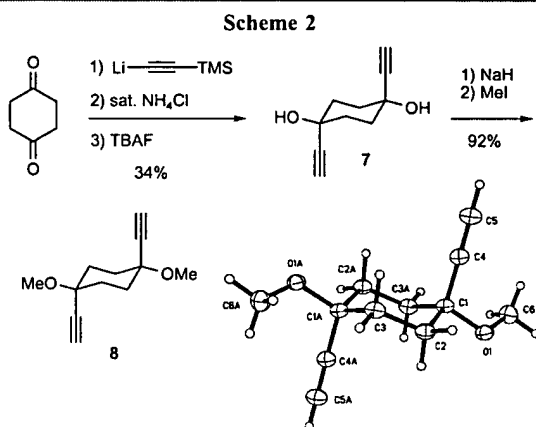


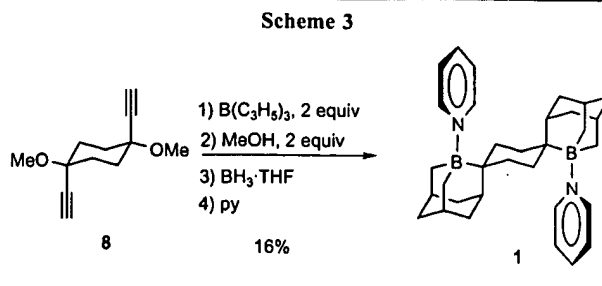
Figure 2. Computational study of the relative stabilities of the isomeric bis-2-spiro-1-boraadamantane frameworks.

prepared according to a modified procedure of Bilton and co-workers (Scheme 2).¹⁴ Diyne **8** is conveniently obtained by the methylation of *trans*-1,4-diethynylcyclohexane-1,4-diol (**7**) by treatment with NaH followed by MeI.



The stereochemistry of the *trans*-isomer was ultimately confirmed by an X-ray diffraction study on a single crystal of **8** (Scheme 2).

With diyne **8** in hand, we proceeded with the allylboron condensation reaction, followed by methanolysis and hydroboration to assemble the bis-2-spiro-1-boraadamantane core of **1** (Scheme 3). Triallylborane was added to solid diyne **8** and immediately heated to 140 °C with stirring. The reaction solution changed from colorless to yellow. After being stirred for 1 h at 140 °C, the solution was cooled to 50 °C, and THF was added to keep the reaction solution liquid upon further cooling to room temperature. Methanol was added (2.7 equiv). The mixture of products could not be purified



by vacuum distillation. Thus, THF and excess methanol were simply removed under high vacuum (0.01 mmHg, 1 d) following methanolysis, and the crude mixture of products was carried into the hydroboration reaction.

The crude, dried methanolysis products were dissolved in THF, and following hydroboration, excess THF was removed by distillation under atmospheric pressure. The resulting crude white foam was dissolved in benzene. Upon the addition of pyridine (2.2 equiv) the solution became orange and mildly exothermed and a fine off-white precipitate formed. The precipitate was filtered, washed with cold benzene, and dried under high vacuum to give the bis-2-spiro-1-boraadamantane·pyridine (**1**) in 16% yield.

A small portion of the fine powder of complex **1** was dissolved in benzene and further purified by chromatography (SiO₂, Hex/benzene 1:1). Crystals of **1** formed incorporating two molecules of benzene from the chromatography solvent for every molecule of **1**. An X-ray diffraction study confirmed the presence of benzene and the structure of **1** (Figure 3).

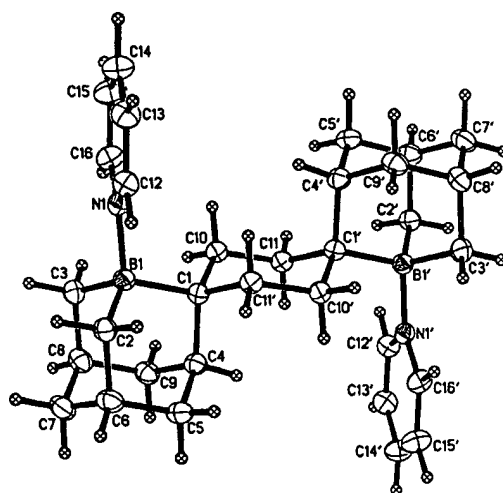
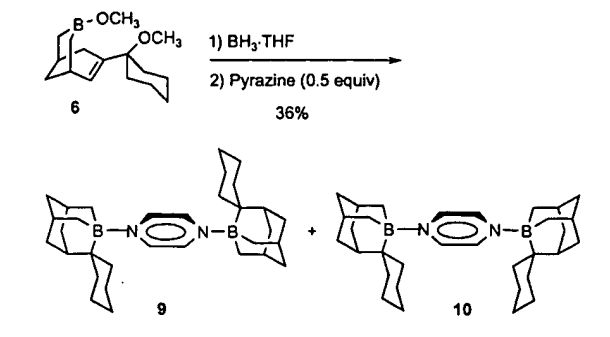


Figure 3. X-ray crystal structure of **1**.

The framework of the bis-2-spiro-1-boraadamantane di-pyridine adduct (**1**) is the *trans*-diequatorial **II** isomer (Figure 2). While other isomeric products of the condensation of

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Scheme 4



triallylborane with diyne **8** may have been produced in the reaction, they were not observed by the procedure used to isolate **1**.

The benzene incorporated into the crystals of **1** evaporates over the course of a few days under atmospheric pressure or a few minutes under high vacuum. However, the remaining off-white solid of **1** is air-stable. While the overall yield of **1** is only 16%, it represents an average yield of 60% per step, and this methodology provides access to a quantity of **1** that can be used for further experimentation.

As a prelude to the use of **1** for the formation of supramolecular assemblies, pyrazine was examined as a di-functional Lewis base for the 2-spiro-1-boraadamantane system (Scheme 4). Following a similar procedure used to synthesize **2**, except substituting pyrazine (0.5 equiv) for pyridine (1 equiv), the bis(2-spiro-1-boraadamantane)·

pyrazine adduct was isolated by precipitation and filtration as a bright vermilion solid. Elemental analysis showed the correct percentages of carbon, hydrogen, and nitrogen. Interestingly, the ^1H NMR spectrum of this compound included two roughly equivalent pyrazine signals and multiple peaks for the boraadamantane fragment. The two pyrazine peaks coalesced at approximately 60 °C (CDCl_3). On the basis of this information, the structures are tentatively assigned as a 1:1 mixture of rotamers **9** and **10**.

In conclusion, we have synthesized the known 2-spiro-1-boraadamantane (**2**) from 1-ethynylcyclohexyl methyl ether (**5**) in comparable yield (41%) to the reported synthesis. This methodology was extended to the synthesis of the novel bis-2-spiro-1-boraadamantane·pyridine (**1**) from *trans*-1,4-diethynyl-1,4-dimethoxycyclohexane (**8**) and determined its molecular structure. Efforts are in progress to utilize the bis-2-spiro-1-boraadamantane framework in supramolecular assemblies.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**, **2**, **5**–**8**, and **10**. X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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